RECEIVED
CENTRAL FAX CENTER
OCT 1 4 2008

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) ...; *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.**' " " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (Emphasis) (MPEP §2112, citations omitted).

Applicants submit that the Examiner has not demonstrated that the phytase described in the Van Ooijen et al. reference teaches that phytase, induces an immune response when administered to an animal as a food or food additive, as required by the instant claims. That is, the Examiner has failed to present extrinsic evidence that "make[s] clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. According to case law, the mere possibility that phytase presented to an animal may induce an immune response is not sufficient to establish inherency.

In view of the above, Applicants submit that all claims are novel in view of the Van Ooigen et al. reference.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 70-72 Under 35 U.S.C. §103

Claims 70-72 are rejected under 35 U.S.C. 103 for allegedly being unpatentable over Van Ooigen in view of Schwoebel et al. (Journal of Biological Chemistry, 266: 7214-7219, 1991) and Walmsley et al. (Current Opinion in Biotechnology, 11: 126-129, 2000).

The Examiner states at page 6 of the Office Action that "Van Ooijen does not teach expression of a heterologous protein inducing immunocontraception."

The Examiner characterizes Schwoebel as teaching ZP antigenic protein that can be used in the development of immunocontraceptive vaccines (see page 6 of the Office Action). The Examiner states at page 6 of the office action that "Walmsley et al. teach transgenic plants expressing heterologous protein of interest which can be used for delivering edible vaccines." The Examiner concludes at page 7 of the Office Action that "[a]t the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to modify the method of making a stable dry homogenate of a transgenic plant as taught by Van Ooijen et al. to substitute the coding sequence encoding phytase of Van Ooijen et al. with Schwoebel et al. coding sequence encoding an antigenic zona pellucida protein to obtain a stable dry homogenate of a transgenic plant comprising high levels of heterologous zona pellucida protein."

Applicants respectfully traverse the rejection.

Van Ooijen et al. relates to expression of phytase in transgenic plants and plants organs.

Schwoebel et al. teach the isolation and characterization of a cDNA encoding zona pellucida protein.

Walmsley et al. teach plants for edible vaccines that are made of non-processed materials. That is, the edible vaccines disclosed in the Walmsley et al. publication are not a "stable dry homogenate" (see for example page 128, left hand column which describes feeding potato cubes to participants), as required by the instant claims. One of skill in the art would appreciate that as of the 2000 date of the Walmsley et al. reference, dry, stable homogenates, for use as vaccines, were not known.

No motivation to combine the references

It is submitted that one of skill in the art would not be motivated to combine the teachings of Van Ooigen, Schwoebel and Walmsley to successfully arrive at the invention as described in the instant claims because none of the references, either alone or in combination, teach or suggest the essential elements of the claims. Indeed, the cited art actually teaches away from the present invention.

Even assuming *arguendo* that the references were combined, they still fail to provide the invention as claimed.

For instance, to establish a *prima facie* case of obviousness the Examiner must identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. (Memo from Margaret A. Focarino Deputy Commissioner for Patent Operations to Technology Center Directors, May 3, 2007). "Often it will be necessary…to look to the interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, to determine whether there was an **apparent reason** to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis **should be made explicit**." (*KSR, Int'l Co. v. Teleflex, Inc.*, 127 S. Ct., 1727, slip opinion at 14) Emphasis added "In view of the guidance provided by the Supreme Court in KSR, an examiner must continue to articulate a reason or rationale to support an obviousness rejection under 35 U.S.C. 103." (Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*)

For at least the reasons set forth herein, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or **motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings** (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a **reasonable expectation of success**. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. Finally, the prior art reference (or references when combined) must teach or suggest **all the claim limitations**. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

The Walmsley et al. reference teaches edible vaccines. It is stated in the reference at page 127, left column that "[t]he success of an edible vaccine requires induction of the mucosal immune system."

The Van Ooigen reference relates to expression of phytase in transgenic plants or plant organs. In particular, the Van Ooigen reference relates to an economical procedure for the production of phytase to be used in animal food (see for example column 3, lines 39-48). The Van Ooigen et al. reference states at column 3, lines 65-67 that:

> "[t]he transgenic plants and plant organs provided by the present invention may be applied to a variety of industrial processes either directly, e.g. in animal food or feedstuffs or alternatively, the expressed phytase may be extracted and if desired, purified before application."

It is also stated at column 9, lines 32-39 of the Van Ooigen et al. reference that:

> "[t]he plants or plant organs containing phytase produced according to the present invention may be used in industrial process requiring the action of a phytase. Examples of such applications are in feed additives for non-ruminants, in soy processing, or in the production of inositol or inositol-phosphates from phytate. Other industrial processes using substrates that contain phytate such as the starch industry and in fermentation industries, such as the brewing industry."

Additionally, the Van Ooigen et al. reference states at column 10, lines 7-10 that:

> "[i]t will be appreciated that the application of phytases, available at a price competitive with inorganic phosphates will increase the degrees of freedom for the compound feed industry to produce a high quality feed."

As discussed above, the Van Ooijen et al. reference teaches a plant system for the production of phytase for use in animal foodstuff. Van Ooijen does not teach or suggest the production of a vaccine. In particular, the Van Ooijen et al. reference does not teach or suggest "a stable dry homogenate of a transgenic plant expressing a heterologous protein comprising an antigen or an antibody wherein **administration of said homogenate to an animal induces an immune response.** Such a composition would be required for a vaccine.

The system described in the Van Ooijen et al. reference is for production of phytase for use in animal foodstuff. One of skill in the art would accept that it would be undesirable to prepare a foodstuff that comprises phytase that induces an immune response when administered to an animal. Therefore, Van Ooijen et al. clearly teaches away from either of a stable dry homogenate of a transgenic plant expressing a heterologous protein or containing a transgenic protein, wherein administration of said homogenate to an animal induces an immune response.

In view of the above, there is no motivation, absent Applicants disclosure to combine the Van Ooigen et al. reference with the Schwoebel et al. and Walmsley et al. references.

Applicants respectfully request withdrawal and reconsideration of the rejection.

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Respectfully submitted,

Dated: October 14, 2008

By Elizabeth

Elizabeth Spar
Registration No.: 45,123
Customer No. 21874
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant

immuno biology 5

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

Charles A. Janeway, Jr.
Yale University School of Medicine

Paul Travers
Anthony Nolan Research Institute, London

Mark Walport
Imperial College School of Medicine, London

Mark J. Shlomchik
Yale University School of Medicine

GARLAND PUBLISHING
ALERE FLAMMAM
Taylor & Francis Group

Vice President: Denise Schanck
Text Editors: Penelope Austin, Eleanor Lawrence
Managing Editor: Sarah Gibbs
Editorial Assistant: Mark Ditzel
Managing Production Editor: Emma Hunt
Production Assistant: Angela Bennett
New Media Editor: Michael Morales
Copyeditor: Len Cegielka
Indexer: Liza Furnival
Illustration and Layout: Blink Studio, London
Manufacturing: Marion Morrow, Rory MacDonald

© 2001 by Garland Publishing.
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means—electronic, mechanical, photocopying, recording, or otherwise—without the prior written permission of the copyright holder.

Distributors:
Inside North America: Garland Publishing, 29 West 35th Street,
New York, NY 10001-2299.
Inside Japan: Nankodo Co. Ltd., 42-6, Hongo 3-Chome, Bunkyo-ku,
Tokyo, 113-8410, Japan.
Outside North America and Japan: Churchill Livingstone, Robert Stevenson House,
1–3 Baxter's Place, Leith Walk, Edinburgh, EH1 3AF.

ISBN 0 8153 3642 X (paperback) Garland
ISBN 0 4430 7098 9 (paperback) Churchill Livingstone
ISBN 0 4430 7099 7 (paperback) International Student Edition

Library of Congress Cataloging-in-Publication Data
Immunobiology : the immune system in health and disease / Charles A. Janeway, Jr. ...
[et al.].– 5th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-8153-3642-X (pbk.)
1. Immunology. 2. Immunity. I. Janeway, Charles. II. Title.

QR181 .I454 2001
616.07'9–dc21
2001016039

This book was produced using QuarkXpress 4.11 and Adobe Illustrator 9.0

Published by Garland Publishing, a member of the Taylor & Francis Group,
29 West 35th Street, New York, NY 10001-2299.

Printed in the United States of America.
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

Immunologists' Toolbox

APPENDIX I

Immunization

Natural adaptive immune responses are normally directed at antigens borne by pathogenic microorganisms. The immune system can, however, also be induced to respond to simple nonliving antigens, and experimental immunologists have focused on the responses to these simple antigens in developing our understanding of the immune response. The deliberate induction of an immune response is known as **immunization**. Experimental immunizations are routinely carried out by injecting the test antigen into the animal or human subject. The route, dose, and form in which antigen is administered can profoundly affect whether a response occurs and the type of response that is produced, and are considered in Sections A-1–A-4. The induction of protective immune responses against common microbial pathogens in humans is often called **vaccination**, although this term is correctly only applied to the induction of immune responses against smallpox by immunizing with the cross-reactive cowpox virus, vaccinia (see Chapter 14).

To determine whether an immune response has occurred and to follow its course, the immunized individual is monitored for the appearance of immune reactants directed at the specific antigen. Immune responses to most antigens elicit the production of both specific antibodies and specific effector T cells. Monitoring the antibody response usually involves the analysis of relatively crude preparations of **antiserum** (plural: **antisera**). The **serum** is the fluid phase of clotted blood, which, if taken from an immunized individual, is called antiserum because it contains specific antibodies against the immunizing antigen as well as other soluble serum proteins. To study immune responses mediated by T cells, blood lymphocytes or cells from lymphoid organs such as the spleen are tested; T-cell responses are more commonly studied in experimental animals than in humans.

Any substance that can elicit an immune response is said to be **immunogenic** and is called an **immunogen**. There is a clear operational distinction between an immunogen and an antigen. An **antigen** is defined as any sustance that can bind to a specific antibody. All antigens therefore have the potential to elicit specific antibodies, but some need to be attached to an immunogen in order to do so. This means that although all immunogens are antigens, not all antigens are immunogenic. The antigens used most frequently in experimental immunology are proteins, and antibodies to proteins are of enormous utility in experimental biology and medicine. Purified proteins are, however, not always highly immunogenic and to provoke an immune response have to be administered with an adjuvant (see Section A-4). Carbohydrates, nucleic acids, and other types of molecule are all potential antigens, but will often only induce an immune response if attached to a protein carrier. Thus, the immunogenicity of protein antigens determines the outcome of virtually every immune response.

The lining of the eye, called the conjunctiva, manifests allergic **conjunctivitis** in sensitized individuals exposed to allergens.

An **allergic reaction** is a response to innocuous environmental antigens, or allergens, due to preexisting antibody or primed T cells. There are various immune mechanisms of allergic reactions, but the most common is the binding of allergen to IgE antibody on mast cells, which causes asthma, hay fever, and other common allergic reactions.

Allergic rhinitis is an allergic reaction in the nasal mucosa, also known as hay fever, that causes runny nose, sneezing, and tears.

Allergy is a symptomatic reaction to a normally innocuous environmental antigen. It results from the interaction between the antigen and antibody or primed T cells produced by earlier exposure to the same antigen.

Alloantigens are classically defined as polymorphisms at the MHC locus; they stimulate intense reactions to allografted tissues, hence their naming.

Two individuals or two mouse strains that differ at the MHC are said to be **allogeneic**. The term can also be used for allelic differences at other loci. Rejection of grafted tissues from unrelated donors usually results from T-cell responses to allogeneic MHC molecules expressed by the grafted tissues. See also **syngeneic**; **xenogeneic**.

An **allograft** is a graft of tissue from an allogeneic or nonself donor of the same species; such grafts are invariably rejected unless the recipient is immunosuppressed.

Alloreactivity describes the stimulation of T cells by MHC molecules other than self; it marks the recognition of allogeneic MHC molecules. Such responses are also called **alloreactions**.

Allotypes are allelic polymorphisms that can be detected by antibodies specific for the polymorphic gene products; in immunology, **allotypic** differences in immunoglobulin molecules were important in deciphering the genetics of antibodies.

An **altered peptide ligand**, or partial agonist, is a peptide, usually closely related to an agonist peptide in amino acid sequence, that induces only a partial response from T cells specific for the agonist peptide.

The **alternative pathway** of complement activation is not triggered by antibody, as is the classical pathway of complement activation, but by the binding of complement protein C3b to the surface of a pathogen; it is therefore a feature of innate immunity. The alternative pathway also amplifies the classical pathway of complement activation.

Anaphylactic shock or **systemic anaphylaxis** is an allergic reaction to systemically administered antigen that causes circulatory collapse and suffocation due to tracheal swelling. It results from binding of antigen to IgE antibody on connective tissue mast cells throughout the body, leading to the disseminated release of inflammatory mediators.

Anaphylatoxins are small fragments of complement proteins, released by cleavage during complement activation. These small fragments are recognized by specific receptors, and they recruit fluid and inflammatory cells to sites of their release. The fragments C5a, C3a, and C4a are all anaphylatoxins, listed in order of decreasing potency *in vivo*.

Peptide fragments of antigens are bound to specific MHC class I molecules by **anchor residues**. These are residues of the peptide that have amino acid side chains that bind into pockets lining the peptide-binding groove of the MHC class I molecule. Each MHC class I molecule binds different patterns of anchor residues, called anchor motifs, giving some specificity to peptide binding. Anchor residues exist but are less obvious for peptides that bind to MHC class II molecules.

Anergy is a state of nonresponsiveness to antigen. People are said to be **anergic** when they cannot mount delayed-type hypersensitivity reactions to challenge antigens, whereas T cells and B cells are said to be anergic when they cannot respond to their specific antigen under optimal conditions of stimulation.

Antagonist peptides are peptides, usually closely related in sequence to an agonist peptide, that inhibit the response of a cloned T-cell line specific for the agonist peptide.

An **antibody** is a protein that binds specifically to a particular substance—its antigen. Each antibody molecule has a unique structure that enables it to bind specifically to its corresponding antigen, but all antibodies have the same overall structure and are known collectively as immunoglobulins or Igs. Antibodies are produced by plasma cells in response to infection or immunization, and bind to and neutralize pathogens or prepare them for uptake and destruction by phagocytes.

Antibody combining site: see **antigen-binding site**.

The **antibody repertoire** or immunoglobulin repertoire describes the total variety of antibodies in the body of an individual.

Antibody-dependent cell-mediated cytotoxicity (ADCC) is the killing of antibody-coated target cells by cells with Fc receptors that recognize the constant region of the bound antibody. Most ADCC is mediated by NK cells that have the Fc receptor FcγRIII or CD16 on their surface.

An **antigen** is any molecule that can bind specifically to an antibody. Their name arises from their ability to generate antibodies. However, some antigens do not, by themselves, elicit antibody production; those antigens that can induce antibody production are called **immunogens**.

Both libraries of cDNA clones in expression vectors and bacteriophage libaries encoding random peptide sequences have been used to identify the targets of specific antibodies and, in some cases, of T cells. Such libraries are termed **antigen display libraries**.

Antigen:antibody complexes are noncovalently associated groups of antigen and antibody molecules that can vary in size from small soluble complexes to large insoluble complexes that precipitate out of solution; they are also known as **immune complexes**.

The **antigen-binding site** of an antibody, or **antibody combining site**, is found at the surface of the antibody molecule that makes physical contact with the antigen. Antigen-binding sites are made up of six hypervariable loops, three from the light-chain V region and three from the heavy-chain V region.

In an **antigen-capture assay**, the antigen binds to a specific antibody, and its presence is detected by a second antibody that must be labeled and directed at a different epitope.

An **antigenic determinant** is the portion of an antigenic molecule that is bound by a given antibody or antigen receptor; it is also known as an epitope.

Influenza virus varies from year to year by a process of **antigenic drift** in which point mutations of viral genes cause small differences in the structure of viral surface antigens. Periodically, influenza viruses undergo an **antigenic shift** through reassortment of their segmented genome with another influenza virus, changing their surface antigens radically. Such antigenic shift variants are not recognized by individuals immune to influenza, so when antigenic shift variants arise, there is widespread and serious disease.

Many pathogens evade the adaptive immune response by **antigenic variation** in which new antigens are displayed that are not recognized by antibodies or T cells elicited in earlier infections.

Antigen presentation describes the display of antigen as peptide fragments bound to MHC molecules on the surface of a cell; T cells recognize antigen when it is presented in this way.

Antigen-presenting cells (APCs) are highly specialized cells that can process antigens and display their peptide fragments on the cell surface together with molecules required for T-cell activation. The main antigen-presenting cells for T cells are dendritic cells, macrophages, and B cells.

Antigen processing is the degradation of proteins into peptides that can bind to MHC molecules for presentation to T cells. All antigens except peptides must be processed into peptides before they can be presented by MHC molecules.